Human Subjects

4.1 Protection of Human Subjects

4.1.1 Risks to Human Subjects

a. Human Subjects Involvement, Characteristics, and Design

Five groups of subjects will be studied: 1) Healthy adults aged 20-35 years old, 2) elite athletes aged 20-35, 3) healthy adults over 65 years of age, 4) healthy adults over 65 engaged in an exercise/fitness program and, 5) patients over 65 with a recent diagnosis of heart failure with preserved ejection fraction (HF-PEF). All subjects will meet the inclusion and exclusion criteria described below. The study will take place at the Martinos Center for Biomedical Imaging at Massachusetts General Hospital in Boston, Massachusetts. The healthy volunteers in group 1 (n=14), group 3 (n=14) and group 4 (n=14) will be recruited from the general public. The elite athletes in group 2 (n=14) will be recruited from the cardiac performance program in the cardiology division of the Massachusetts General Hospital (MGH). The patients in group 5 (n=14) with HF-PEF will be recruited from the general cardiology and heart failure services at the MGH. The MRI scans will be performed on a commercial 3 Tesla scanner (Skyra, Siemens Medical) using the manufacturer's product thoracic coil. During the scan the subjects will be asked to perform multiple breatholds as well as transient isometric handgrip.

Inclusion Criteria

1. Group 1: Healthy adult males and females aged 20-35.
2. Group 2: Elite male and female athletes, aged 20-35, currently participating in competitive swimming, rowing, cycling or running at the varsity level or higher. These athletes will be recruited from the many colleges in the Boston area via the cardiac performance center at the MGH, which has established links with these collegiate athletic programs.
3. Group 3: Healthy adult males and females over 65 years of age.
4. Group 4: Healthy adult males and females over 65 engaged in a regular exercise program (3 sessions per week of >30 minutes each) for at least the last 6 months.
5. Group 5: Patients over 65 with a diagnosis of HF-PEF within the last 3 months. These patients will a) have no evidence of aortic stenosis b) have well controlled blood pressure (SBP < 130) for at least the last 12 months, c) have no evidence of an infiltrative cardiomyopathy and, d) have a BMI < 30.

Exclusion Criteria (All Groups)

a. Known contraindication to MRI
    I. The standard list of contraindications to MRI in research subjects in the Martinos Center will be used. Contraindications of particular relevance to the patients with HF-PEF include: Decompensated heart failure with the inability to breath lying flat, pacemakers, implantable defibrillators, and implantation of a coronary artery stent within 6 weeks before MRI (unless the stent is a MRI-inert chromium-cobalt stent).
b. Known arrhythmia such as atrial fibrillation
c. Highly irregular heart beat
d. Uncontrolled angina
e. Hemodynamic instability (Systolic BP les than 100 or greater than 160)
f. Decompensated heart failure (inability to lie flat and perform a breathold).
g. Body mass index (BMI) >30.
h. Aortic stenosis
i. Hypertension (SBP > 130) during the last 12 months
j. Hypertrophic cardiomyopathy

k. Infiltrative cardiomyopathy (amyloid, sarcoid, hemachromatosis)
l. Recent surgery (within the last 3 months)
m. Prior stroke with residual deficit
n. Presence of liver or respiratory failure
o. Pregnancy
p. Nursing mothers

b. Sources of Materials

All data collected on study participants will be obtained and managed specifically for research purposes. The types of data to be collected will include 1) age, 2) metrics of fitness and exercise performance such as body weight and amount of exercise performed, and 3) MR images. In the case of those patients with HF-PEF the following data will also be obtained: Last episode of heart failure, last echocardiogram (ejection fraction, ventricular dimensions, valvular lesions) and presence/absence of hypertension. No personal identifiers will appear on the MR images or the data forms, which will be labeled only with a study ID number.

Patient identifying information will not be stored on the study databases. Within study databases, participants will be identified by ID number only. Only one data file will contain the linkage of subject identity, subject ID number, and group assignment. This file will be maintained using a limited access, password-protected database on a password-protected desktop computer. Study personnel and appropriate oversight organizations (IRB, NIH officers) will have access to the study databases as needed. MRI safety forms will be completed on paper. All completed paper forms containing data will be kept in a secure, locked filing cabinet located at the Martinos Center.

c. Potential Risks

The risks associated with MRI are minimal and include claustrophobia and mild discomfort. There are no specific risks to the acquisition of diffusion tensor MRI (DTI) data in the heart. The standard safety precautions with respect to MRI safety will apply. The risks associated isometric handgrip are also minimal and this procedures has been frequently performed in similar settings.

4.1.2 Adequate Protection against Risks

a. Recruitment and Informed Consent

The healthy volunteers in group 1 (n=14), group 3 (n=14) and group 4 (n=14) will be recruited from the general public. The elite athletes in group 2 (n=14) will be recruited from the cardiac performance program in the cardiology division of the Massachusetts General Hospital (MGH). The patients in group 5 (n=14) with HF-PEF will be recruited from the general cardiology and heart failure services at the MGH. Advertisements and flyers will be placed in approved public locations and in the outpatient offices of the cardiac performance and heart failure services. A contact number will be provided on the flyer for those volunteers who wish to participate to call. Digital advertisements will also be placed on approved websites within the hospital, which have been designed specifically to assist in study recruitment. Further information will be provided to the potential volunteer, and initial screening will be performed, when they call.

Patients and normal subjects who agree to participate will then be registered and informed consent will be obtained at the Martinos Center. The informed consent document will be approved by the IRB at Partners HealthCare, which covers Massachusetts General Hospital, prior to subject recruitment. The informed consent interview will be conducted by the study staff and will include a verbal and written explanation of the study, including the purpose, testing procedures, time commitment, inclusion/exclusion criteria, risks and benefits, alternative approaches, confidentiality, compensation, study personnel contacts, and required regulatory information. All individuals will be given the opportunity to ask questions. Once all questions and concerns are addressed to the participant's satisfaction, the participant will sign the consent form. Only subject themselves will sign the consent form. Following informed consent, the study participant will be assigned an anonymous

study identification number. From this point forward, only the study ID number will be used to identify the individual, and the signed informed consent document will be stored securely and separately from all other research materials.

In accordance with NIH guidelines, efforts will be made to attain a mix of study participants, in terms of gender and racial/ethnic representation (see below for more detail). Children will not be included because the principal focus of this study is to detect the influence of advanced age on the properties of the myocardium.

b. Protection Against Risks

To ensure that no patient/volunteer with a contraindication to MRI is scanned, MRI safety screening will be performed for a second time before the subject enters the scan room. This will include the completion of a safety screening form and the use of a metal detector. All scans will be performed on a commercial FDA-approved scanner (Skyra, Siemens Medical) with product coils and sequence protections. The ECG will be monitored throughout the scan and particularly during isometric handgrip. The subject and study staff will also be in full voice contact throughout the scan. If any concern of discomfort or instability arises during the scan, the patient will be removed from the magnet and treated accordingly. Two licensed and ACLS-certified physicians will be present within the building throughout the scan.

4.1.3 Potential Benefits

The study has the potential to provide direct benefits to the participants with minimal risk. By measuring the structural properties of the heart with diffusion tensor MRI, we will be able to provide direct feedback to the participants and their contact physicians about the health of their myocardium. This information could be used to guide lifestyle, diet and medication changes.

4.1.4 Importance of the Knowledge to Be Gained

This study will increase knowledge in three important areas. The first area is MR imaging technology. The experience gained and advances made with novel DTI techniques will be applicable to a broad array of cardiovascular conditions. The second area in which knowledge will be gained is that of the physiology and pathophysiology of aging. The results of this study will provide important information about the microstructural response of the heart to aging and how this is modulated by exercise. The final area of knowledge gain will be an enhanced understanding of the structural properties of the myocardium that predispose to the development HF-PEF. The use of DTI in this study will help elucidate the pathophysiology of HF-PEF. Ultimately, the knowledge gained in this trial could transform the way that HF-PEF is diagnosed and followed clinically.

4.1.5 Data Safety Monitoring Plan

The study team will meet at least monthly to assess progress and results. Adverse events will be reported according to FDA guidelines, and reports will be sent to Massachusetts General Hospital (Partners Research Management) IRB as required. The principal investigator will be notified when an adverse event occurs and will determine the attribution and relatedness of each adverse event. An internal safety monitoring board will also be constructed and will consist of cardiologists and radiologists. All adverse events will be reviewed by the key personnel and by this safety monitoring board.

4.1.6 ClinicalTrials.gov

The study will be registered with ClinicalTrials.gov.